Caffeine Consumption During Pregnancy and Fetal Growth

ABSTRACT

Background: The purpose of this study was to examine the association between maternal caffeine consumption and low birthweight, intrauterine growth retardation, and prematurity, adjusting for multiple confounders.

Methods: Data obtained from birth certificates and interviews on 1,230 women with singleton live births were analyzed to evaluate the potential influence of caffeine consumption during the first trimester on fetal growth.

Results: The crude odds ratio for intrauterine growth retardation in infants of women reporting heavy caffeine consumption (>300 mg/day) was 3.86 (95% CI = 1.80, 8.40) which decreased to 2.90 (95% CI = 1.23, 6.87) after controlling for confounding factors. The adjusted odds ratio for low birthweight and heavy maternal caffeine consumption was also elevated (OR = 2.05; 95% CI = 0.86, 4.88). Women who reduced their caffeine intake from greater than 300 mg/day to less than that early in pregnancy had lower risks of delivering infants with either intrauterine growth retardation or low birthweight than women who continued to consume that amount. Preterm delivery appeared to be unrelated to caffeine consumption.

Conclusions: Taken together with studies reporting similar findings, these results suggest that heavy caffeine consumption increases the risk for fetal growth retardation. (*Am J Public Health* 1991;81:458–461)

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Introduction

In 1980, the United States Food and Drug Administration warned pregnant women to restrict their intake of caffeine based on increased adverse reproductive outcomes in animals.[1] Since then, a number of epidemiologic studies have examined the association between caffeine intake and low birthweight (LBW) and a few have investigated its relationship to intrauterine growth retardation (IUGR). In a prospective study, Martin and Bracken found a more than two-fold risk of LBW in term deliveries associated with caffeine intake of 151–300 mg daily during the first trimester and a greater than four-fold risk associated with intake of >300 mg daily.[2] A case-control study which combined cases of LBW and IUGR found an increased risk associated with caffeine intake greater than 300 mg daily during the first trimester (OR = 2.94; 95% CI = 0.89, 9.65).[3] In addition, a retrospective study demonstrated a relationship between caffeine consumption of greater than 300 mg daily and reduced birthweight.[4] In contrast, a prospective[5] and a large retrospective[6] study found no relationship between caffeine or coffee consumption and reduced birthweight, respectively.

Methods

Participants and Questionnaires

Participants were women selected as controls in a case-control study of spontaneous abortion (SAB); a detailed description of subject selection and recruitment is presented elsewhere.[7] Birthweight was obtained from birth certificates. LBW was defined as birthweight less than 2,500 grams. Gestational age was calculated from the date of the last menstrual period (LMP) to the baby's birth date, as reported on interview. IUGR was defined as weight less than the tenth percentile of the mean weight at each gestational week using standards developed for California (all races and sexes combined).[8] Preterm delivery was defined as gestational age of less than 37 weeks.

The interview was conducted by telephone, on average, nine months after birth. For caffeinated beverage consumption questions (caffeinated coffee, tea and soft drinks), the participant was asked the amount consumed during the month before pregnancy, if it changed during pregnancy and, if so, when and to what amount. This information was used to calculate each participant's average consumption during the first trimester of pregnancy, based on her consumption each week. Caffeine consumption was calculated by summing the average amount of caffeinated coffee, tea, and soft drinks consumed, assuming a caffeine content of 107 mg/cup, 34 mg/cup, and 47 mg/can, respectively.[9]

The analyses were limited to singleton births (n = 1,252). Women who were missing information on birthweight (n = 1) or on caffeine consumption (n = 8) or whose calculated gestational age was 45 weeks or more (n = 13) were excluded from the analyses, leaving 1,230 singleton live births.

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Statistical Analyses

We examined maternal characteristics within four categories of caffeine consumption consistent with those from previous studies:[2-4] no caffeine; average caffeine use of 1–150 mg/day (light use); 151–300 mg/day (moderate use); and >300 per/day (heavy use). Analysis of variance was used to determine whether mean birthweights or mean gestational ages differed by category of caffeine use. Unadjusted odds ratios (OR), confidence intervals (CI) and chi-square trend tests were calculated for three levels of caffeine consumption with no consumption as the reference group.

Adjusted odds ratios were calculated using logistic regression with indicator variables for light, moderate, and heavy caffeine use. Caffeine was also modeled as a continuous variable. Since results were similar, categorical variables are presented for ease of comparison to other studies.

Confounding variables were included if they were strongly related to LBW or related to both LBW and caffeine use. The following maternal characteristics were entered into the LBW models: maternal age (≤34, >34); parity (0, ≥1); race (White, Hispanic, other); hypertension during pregnancy (yes, no); cigarettes smoked (0, 1–10 daily, ≥11 daily); and alcohol consumed (0, 1–3 drinks per week, ≥4 drinks per week). Separate models were run to test for an interaction between caffeine and tobacco use and between caffeine and alcohol consumption.

Reductions in caffeine consumption early in pregnancy were examined to determine whether these changes might affect fetal growth. Crude and adjusted odds ratios were calculated separately for women who did and did not reduce their intake from greater than an average of 300 mg/day to less than that amount within six weeks of their LMP. The reference group for these analyses was women with no caffeine consumption. Six weeks post-LMP was chosen as the time to evaluate the effect of reducing caffeine consumption because it approximates the earliest time that a woman realizes she is pregnant.

The strategy outlined above was followed for the univariate and multivariate analyses of caffeine consumption and IUGR or prematurity. The following covariates were entered in the models for IUGR: hypertension, cigarettes, and alcohol, as defined above. Variables included in the models for prematurity were: education (less than high school, high school graduate, some college, college graduate), race, hypertension, cigarettes and alcohol.

Results

Characteristics of Study Population

Table 1 presents population characteristics by four categories of caffeine consumption. The following variables were associated with increased caffeine consumption: multiparity, one or more therapeutic abortions, being employed, and use of cigarettes or alcohol. Ethnicity other than White or Hispanic was associated with decreased caffeine consumption, as was being more highly educated.

Association with LBW, IUGR

Overall, the risk factors for LBW were consistent with previous studies.[10] Nulliparous women over 34 years of age were at increased risk for delivering a LBW infant. Prior stillbirth, hypertension during the current pregnancy, smoking more than 10 cigarettes per day, or drinking four or more alcoholic drinks each week were associated with LBW. Race was also associated with LBW; Whites were least likely to deliver a LBW infant. Women who did not have insurance coverage for prenatal care (a surrogate measure for low socioeconomic status) were also at increased risk for LBW. IUGR was more common among women with hypertension during pregnancy, smoking more than 10 cigarettes per day, or drinking four or more alcoholic drinks per week.

Association of LBW and Caffeine

The mean birthweights for no, light, moderate, and heavy caffeine use were 3327 grams, 3311 grams, 3288 grams and 3170 grams respectively. Table 2 presents the unadjusted and adjusted odds ratios for LBW by caffeine consumption. A dose-response effect with increasing consumption of caffeine was observed (χ^2 trend = 4.03, p = 0.05). The crude risk for those with the heaviest level of caffeine consumption was twice that in the unexposed group. Adjusting for covariates resulted in a slightly lowered measure of association. Including interaction terms for cigarette smoking and caffeine consumption and for alcohol and caffeine consumption did not alter these estimates. Women who reduced their heavy caffeine consumption (within six weeks of their LMP) had a lower risk of delivering a LBW infant (adjusted OR = 0.65; 95% CI = 0.20, 2.11) than those women who continued to drink this amount (adjusted OR = 3.05; 95% CI = 1.09, 8.51).

Association of IUGR and Caffeine

The association of caffeine and IUGR increased with amount (χ^2 trend = 11.42, p = 0.0007), with a doubled risk for medium consumers and almost a four-fold risk for heavy consumers (Table 3). The adjusted OR for heavy caffeine consumption remained elevated, although decreased (OR = 2.90). Addition of interaction terms for cigarette smoking and caffeine consumption and for alcohol and caffeine consumption did not alter these estimates. Women who reduced their heavy caffeine consumption had a lower risk of IUGR (adjusted OR = 1.58; 95% CI = 0.56, 4.42) than women who continued this level of caffeine intake (adjusted OR = 3.74; 95% CI = 1.34, 10.41).

Association of Preterm Delivery and Caffeine

Mean gestational age varied little by caffeine use. Although the crude odds ratio for preterm delivery and heavy caffeine consumption was somewhat elevated (OR = 1.76), this estimate was decreased after multivariate adjustment (adjusted OR = 1.31; 95% CI = 0.63, 2.69). Women who continued their heavy caffeine consumption had a higher risk of preterm delivery (adjusted OR = 1.72; 95% CI = 0.70, 4.24) than women who reduced their intake (adjusted OR = 1.10; 95% CI = 0.50, 2.43).

Discussion

This study indicated elevated risks for IUGR and for LBW associated with heavy caffeine consumption which continued beyond the sixth week of pregnancy. Recall bias is an unlikely explanation of these findings since little relationship between preterm delivery and caffeine consumption was seen. Consistency of reporting of caffeinated beverage consumption was examined in a smaller case-control study of SAB,[11] in which caffeine consumption was asked as in this study. Substantial agreement for reports of caffeine consumption between interviews which were six months apart was found; approximately 77 percent of women's responses agreed to within one cup.[11] In addition, reporting of coffee consumption has recently been shown to have good reliability over a period of time which ranged from nine days to 6.5 years.[12]

TABLE 1—Distribution of Maternal Characteristics by Level of Caffeine Consumption during Pregnancy, Santa Clara County, California, 1986–87

Variables*	Total	Daily Caffeine Consumption: None	Light (1–150 mg)	Moderate (151–300 mg)	Heavy (>300 mg)	p-value
Subjects (N)	1230	378	609	165	78	
Subjects (%)	100	30.7	49.5	13.4	6.4	
Maternal Age (years)						
≤34	1072	30.6	50.5	13.1	5.8	p = 0.11
>34	158	31.7	43.0	15.2	10.1	
Parity						
0	507	31.2	53.3	12.2	3.3	p = 0.002
≥1	719	30.6	46.7	14.3	8.3	
Previous Spontaneous Abortions						
0	982	31.0	50.2	13.3	5.5	p = 0.14
≥1	244	30.3	46.3	13.9	9.4	
Previous Therapeutic Abortions						
0	969	32.9	48.8	12.7	5.6	p = 0.006
≥1	257	24.0	51.8	16.3	8.9	
Previous Stillbirths						
0	1197	30.9	49.5	13.4	6.2	p = 0.83
≥1	29	27.6	48.3	13.8	10.3	
Race						
Hispanic	320	28.1	50.3	15.0	6.6	p = 0.002
White	639	27.8	51.0	13.5	7.7	
Other	270	40.7	45.2	11.1	3.0	
Education						
<High School	202	27.7	49.0	16.8	6.5	p = 0.001
High School Graduate	357	23.3	51.5	15.7	9.5	
Some College	346	35.2	48.0	11.3	5.5	
College Graduate	325	36.0	49.2	11.1	3.7	
Marital Status						
Together	1123	31.0	49.8	13.2	6.0	p = 0.32
Apart	107	28.0	46.7	15.0	12.3	
Insurance Coverage						
Yes	1098	30.1	50.0	13.6	6.3	p = 0.60
No	132	35.6	45.5	12.1	6.8	
Employment						
Yes	870	27.9	51.4	14.0	6.7	p < 0.001
No	359	37.6	45.1	12.0	5.3	
Hypertension during Pregnancy						
Yes	45	33.3	37.8	20.0	8.9	p = 0.33
No	1183	30.6	50.0	13.2	6.2	
Cigarettes/day						
0	998	34.8	51.0	10.2	4.0	p < 0.001
1–10	146	18.5	42.5	26.7	12.3	
≥11	86	4.6	44.2	27.9	23.3	
Alcoholic Drinks/day						
0	566	39.2	45.9	20.8	4.2	p < 0.001
1–3	598	24.9	52.7	15.5	6.9	
≥4	62	9.7	53.2	17.7	19.4	

*Numbers for some variables do not total 1,230 because of missing data. Percentages for some variables do not total 100 because of rounding errors.

In these analyses, pre-pregnancy weight and pregnancy weight gain—maternal characteristics known to be associated with fetal growth—were not collected.[10] In Martin and Bracken's study, although caffeine users tended to gain less weight than nonusers, the caffeine risk estimates were only slightly reduced when weight gain was entered into the logistic models.[2] Birthweight and IUGR may also be influenced by exposures occurring during the second and third trimesters which were not ascertained. However, a case-control study found that average coffee and tea consumption in the second and third trimesters did not differ appreciably from that in the first trimester.[13]

There are two potential sources of exposure misclassification. We did not collect information on caffeine intake from caffeinated drug use, chocolate, or cocoa. This bias is unlikely to be substantial since for most pregnant women the largest source of caffeine intake is coffee.[4,14] Nevertheless, our measures of caffeine consumption were crude, given the substantial variation in caffeine content with method of beverage preparation and volume of serving.[9]

Our results suggest an effect of caffeine consumption of greater than 300 mg/daily on IUGR and LBW but not preterm delivery. These findings are consis-

TABLE 2—Odds Ratios for LBW and Caffeine Consumption, Santa Clara County, California, 1986–87

Caffeine Intake*	Case	Control	Crude OR	95% CI†	Adjusted OR††	95% CI†
0	27	351	1.00	—	1.00	—
1–150	34	575	0.77	(0.46, 1.29)	0.78	(0.45, 1.35)
151–300	14	151	1.21	(0.63, 2.38)	1.07	(0.51, 2.21)
>300	12	66	2.36	(1.17, 4.93)	2.05	(0.86, 4.88)
Total	87	1143				

*Average consumption during first trimester, including any changes in habit.
†Confidence Interval calculated by Cornfield's method (using Epistat).
††Adjusted by logistic regression for age, parity, race, hypertension during pregnancy and cigarette and alcohol consumption during pregnancy.

TABLE 3—Odds Ratios for IUGR and Caffeine Consumption, Santa Clara County, California, 1986–87

Caffeine Intake*	Case	Control	Crude OR	95% CI†	Adjusted OR††	95% CI†
0	17	361	1.00	—	1.00	—
1–150	41	568	1.53	(0.85, 2.68)	1.45	(0.80, 2.63)
151–300	14	151	1.97	(0.96, 4.08)	1.58	(0.73, 3.41)
>300	12	66	3.86	(1.80, 8.40)	2.90	(1.23, 6.87)
Total	84	1146				

*Average consumption during first trimester, including any changes in habit.
†Confidence Interval calculated by Cornfields Method (using Epistat).
††Adjusted by logistic regression for hypertension during pregnancy and cigarette and alcohol consumption.

tent with those of other studies[2–4] and are biologically plausible. Caffeine is readily absorbed from the digestive tract and freely crosses the placenta.[15,16] Caffeine increases intercellular cyclic 3′,5′-adenosine monophosphate (cyclic AMP), which may directly interfere with fetal development.[17] A dose of 200 mg of caffeine significantly decreases blood flow in placental villi,[18] probably through vasoconstriction.[19] Any reduction in uteroplacental circulation is strongly associated with decreased fetal growth.[10] IUGR[20] and LBW[10] are associated with increased risks of perinatal mortality and morbidity. Clinicians should counsel women early in pregnancy about reducing caffeine intake to below 300 mg daily. □

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References

1. Goyan JE: Food and Drug Administration, news release No. P80-36. Washington, DC: FDA, September 4, 1980.
2. Martin T, Bracken M: Association of low birth weight and caffeine consumption during pregnancy. Am J Epidemiol 1987; 126:813–821.
3. Caan BJ, Goldhaber MK: Caffeinated beverages and low birthweight: A case-control study. Am J Public Health 1989; 79:1299–1300.
4. Watkinson B, Fried PA: Maternal caffeine use before during and after pregnancy and effects upon offspring. Neurobehav Tox Teratol 1985; 7:9–17.
5. Brooke OG, Anderson HR, Bland JM, Peacock JL, Stewart CM: Effects on birthweight of smoking, alcohol, caffeine, socioeconomic factors, and psychosocial stress. Br Med J 1989; 298:795–801.
6. Linn S, Schoenbaum SC, Monson RR, Rosner B, Stubblefield PG, Ryan KJ: No association between coffee consumption and adverse outcomes of pregnancy. N Engl J Med 1982; 306:141–145.
7. Windham GC, Fenster L, Swan SH, Neutra RR: Use of video display terminals during pregnancy and the risk of spontaneous abortion, low birthweight, or intrauterine growth retardation. Am J Ind Med 1990; 18:675–688.
8. Williams RL, Creasy RK, Cunningham GC, Hawes WE, Norris FD, Tashiro M: Fetal growth and perinatal viability in California. Obstet Gynecol 1982; 59:624–632.
9. Bunker ML, McWilliams M: Caffeine content of common beverages. J Am Dietet Assoc 1979; 74:28–32.
10. Institute of Medicine, Division of Health Promotion and Disease Prevention, Committee to Study the Prevention of Low Birthweight: Preventing Low Birthweight. Washington, DC: National Academy Press, 1985.
11. Fenster L, Swan SH, Windham GC, Neutra RR: Assessment of reporting consistency in a case-control study of spontaneous abortions. Am J Epidemiol (In press) 1991; 133.
12. Kelly JP, Rosenberg L, Kaufman DW, Shapiro S: Reliability of personal interview data in a hospital-based case-control study. Am J Epidemiol 1990; 131:79–90.
13. Berkowitz GS, Holford TR, Berkowitz RL: Effects of cigarette smoking, alcohol, coffee and tea consumption on preterm delivery. Early Hum Dev 1982; 7:239–250.
14. Bracken MB, Bryce-Buchanan C, Silten R, Srisuphan W: Coffee consumption during pregnancy. N Engl J Med 1982; 306:1548–1549.
15. Mirkin BL, Singh S: Placental transfer of pharmacologically active molecules. *In:* Mirkin BL, (ed): Perinatal Pharmacology and Therapeutics. New York: Academic Press, 1976.
16. Goldstein A, Warren R: Passage of caffeine into human gonadal and fetal tissues. Biochem Pharmac 1962; 17:166–168.
17. Morris MB, Weinstein L: Caffeine and the fetus: Is trouble brewing? Am J Obstet Gynecol 1981; 140:607–610.
18. Kirkinen P, Jouppila P, Koivula A, Vuori J, Puukka M: The effect of caffeine on placental and fetal blood flow in human pregnancy. Am J Obstet Gynecol 1983; 147:939–942.
19. Weathersbee PS, Lodge JR: Caffeine: its direct and indirect influence on reproduction. J Reprod Med 1977; 19:55–63.
20. Creasy RK, Resnik R: Intrauterine growth retardation. *In:* Creasy RK (ed): Maternal-fetal Medicine: Principles and Practice. Philadelphia: WB Saunders Company, 1989; Ch 31.